CHRONIC TOXICITY SUMMARY

PROPYLENE GLYCOL MONOMETHYL ETHER

(1-Methoxy-2-propanol; 1-methoxypropanol; Propapsol solvent M)

CAS Registry Number: 107-98-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**7,000 µg/m^3** (2000 ppb) .
Critical effect(s)	Liver effects in rats
Hazard index target(s)	Alimentary system (liver)

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless liquid
Molecular formula	$C_4H_{10}O_2$
Molecular weight	90.14
Density	0.962 g/cm^3 @ 20°C
Boiling point	118-118.5°C
Melting point	-96.7°C
Vapor pressure	11.8 torr @ 25°C
Solubility	Soluble in water, methanol, ether, and other organic solvents
Conversion factor	1 ppm = 3.69 mg/m^3 at 25°C

III. Major Uses or Sources

Propylene glycol monomethyl ether (PGME) is used as a solvent for cellulose, acrylics, dyes, inks and stains (HSDB, 1995). Thus, the primary use of PGME is in lacquers and paints. Use of PGME is anticipated to increase due to its low systemic toxicity. The annual specific statewide industrial emissions of PGME from facilities reporting under the Air Toxics Hot Spots Act in California, based on the most recent inventory, were estimated to be 205,769 pounds (CARB, 1999). (Many industries did not estimate emissions of specific glycol ethers so that in 1998 there were also emitted 2,922,744 pounds of the general category glycol ethers, some of which may be PGME.)

IV. Effects of Exposures on Humans

No reports or studies of human toxicity following chronic exposure to PGME were located in the literature. Slight eye irritation was reported by two of six human volunteers exposed to 100 ppm PGME for 2 hours (Stewart *et al.*, 1970). These subjects were exposed for a total of 3 1/2 hours during which no decrement in visual acuity, coordination, neurological responses or reaction

time was measured. The same experiment exposed 23 subjects to 250 ppm PGME. After 15 to 30 minutes of exposure, 8/23 reported eye irritation and 3/23 reported throat irritation; lacrimation was observed in 3/23 subjects. Three subjects each reported one of the following symptoms: irritation, headache, and nausea. While the subjects frequently reported the odor to be objectionable upon first entering the chamber, the odor was usually undetectable by the end of the exposure. Clinical chemistry and urinalysis completed following exposure was not altered as compared to pre-exposure measurements.

V. Effects of Exposures on Animals

Male and female rats (10 per sex per concentration) and rabbits (7 per sex per concentration) were exposed by inhalation to 300, 1000, or 3000 ppm PGME 5 hours per day, 5 days per week for 13 weeks (Landry *et al.*, 1983). Relative liver weights were statistically significantly higher than controls in both male and female rats exposed to 3000 ppm PGME. Hepatocellular hypertrophy was observed upon histopathologic examination of high dose females. The authors conclude that these effects are the result of physiologic adaptation rather than a manifestation of toxicity. The key observation in this study was sedation of rats and rabbits exposed to 3000 ppm PGME. The sedative effects were no longer apparent after 1-2 weeks of exposure.

Similar findings of mild CNS depression were observed by Hanley *et al.* (1984). Pregnant rats and rabbits were exposed to 500, 1500, or 3000 ppm PGME 6 hours per day either days 6-15 or days 6-18 of gestation, respectively. During the first 4-5 days of exposure, rats in the 3000 ppm PGME exposure group were lethargic and moderately ataxic. Statistically significant decreases in food consumption and maternal body weight gain were also observed during this period. A statistically significant increase in the incidence of delayed sternebral ossification was observed in the 3000 ppm exposure group. Rabbits exposed to 3000 ppm exhibited mild lethargy during the first 1-2 days of exposure with rapid post-exposure recovery. Overall maternal weight gain during the exposure (days 6-18 of gestation) was statistically significantly lower than controls.

No significant effect on fetal birth weight or on pup survival indices (e.g., proportion of pups surviving to day 3 post-delivery) was noted following exposure of pregnant rats to 200 or 600 ppm PGME 6 hours per day on days 6-17 of gestation (Doe *et al.*, 1983). Male rats were exposed to 200 or 600 ppm PGME 6 hours per day for 10 consecutive days. No significant effects on testicular weight or pathology were observed.

Increased liver and kidney weights were observed in male and female rats (10 per sex per concentration) following exposure to 6000 ppm for 7 hours per day, for 81 exposures over a 114-day period (Rowe *et al.*, 1954). No histopathological abnormalities were observed at necropsy.

Ciezlak et al. (1998) evaluated the potential chronic toxicity/oncogenicity and the response of liver and kidney tissue of Fischer 344 rats to propylene glycol monomethyl ether (PGME) at targeted vapor concentrations of 0, 300, 1000 or 3000 ppm. Groups of 50 male and female rats per sex were whole-body exposed under dynamic airflow conditions for 6 hours/day, 5 days/week for up to 2 years. Parameters evaluated included the general appearance and demeanor of animals, in-life body weights, survival, hematology, urinalysis and clinical

chemistry determinations, survival, selected organ weights, gross and microscopic pathologic changes and tumor incidence. (The metabolic and morphological bases for PGME-induced sedation, hepatic hypertrophy and renal toxicity were characterized in separate groups of male and female rats exposed to PGME for 6, 12 or 18 months. Hepatic enzyme induction and cellular proliferation, as well as renal cellular proliferation and accumulation of $alpha_{2u}$-globulin (males only) in the kidneys, were conducted in these separate groups of animals.)

PGME-induced sedation at 3000 ppm resolved in all animals during the second week of exposure in conjunction with the appearance of adaptive changes in the liver (cytochrome P450 induction and hepatocellular proliferation). Cytochrome P450 (pentoxyresorufin O-demethylase) activities dropped to near control concentrations by week 52, coinciding with a return of sedation at 3000 ppm PGME. In male rats, the loss of metabolic adaptation was followed by a dose-related increase in altered hepatocellular foci after two years of exposure to 1000 or 3000 ppm PGME. The kidney toxicity observed in male rats was confirmed immunohistochemically as an $alpha_{2u}$-globulin nephropathy. No statistically-identified increases in tumors were observed in any tissue. The authors established a NOEL of 300 ppm PGME for the study.

Ethylene glycol methyl ether (EGME), a structurally related compound, exerts considerable toxicity on the blood, thymus, testes, and developing fetus. The toxicity of EGME has been linked to its primary metabolite, methoxyacetic acid. Recent comparative toxicity and metabolism studies (Miller *et al.*, 1983, Miller *et al.*, 1984) indicate that the relatively low systemic toxicity exerted by PGME is due to its different metabolites. Following a single oral dose of PGME, the key urinary metabolites identified in rats were propylene glycol and the sulfate and glucuronide conjugate of PGME (Miller *et al.*, 1983).

VI. Derivation of Reference Exposure Level

Study	Ciezlak *et al.*, 1998
Study population	Fischer 344 rats (50/sex/concentration)
Exposure method	Discontinuous whole-body inhalation (0, 300, 1000, or 3000 ppm)
Critical effects	Increased eosinophilic foci of altered hepatocytes
LOAEL	1000 ppm
NOAEL	300 ppm
Exposure continuity	6 hours per day, 5 days per week
Average experimental exposure	54 ppm for NOAEL group (300 x 6/24 x 5/7)
Human equivalent concentration	54 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	104 weeks
LOAEL factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	2 ppm (2000 ppb, 7 mg/m^3, 7000 $\mu g/m^3$)

VII. Data Strengths and Limitations for Development of the REL

Strengths of the PGME RfC include the observation of a NOAEL and a LOAEL in the same study, and the availability of chronic exposure studies involving multiple concentrations. A major area of uncertainty is the lack of human data.

VIII. References

AIHA. 1989. American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron, OH: AIHA.

CARB. 1999. Air toxics emissions data collected in the Air Toxics Hot Spots Program CEIDARS Database as of January 29, 1999.

Ciezlak FS, Crissman JW, Stott WT, and Corley RA. 1998. Propylene glycol monomethyl ether: a two-year vapor inhalation chronic toxicity/oncogenicity study and evaluation of hepatic and renal cellular proliferation, P450 enzyme induction and protein droplet nephropathy in Fischer 344 rats. Dow Chemical Company, Midland, MI.

Doe JE, Samuels DM, Tinston DJ, de Silva Wickramaratne GA. 1983. Comparative aspects of the reproductive toxicology by inhalation in rats of ethylene glycol monomethyl ether and propylene glycol monomethyl ether. Toxicol. Appl. Pharmacol. 69:43-47.

Gingell R, Boatman RJ, Bus JS, Cawley TJ, Knaak JB, Krasavage WJ, Skoulis NP, Stack CR, and Tyler TR. 1994. Chapter 31: Glycol ethers and other selected glycol derivatives. In: Patty's Industrial Hygiene and Toxicology. Fourth Edition, Vol. 2, Part D. Clayton GD, and Clayton FE, eds. New York: John Wiley and Sons, Inc.

Hanley TR, Calhoun LL, Yano BL, and Rao KS. 1984. Teratologic evaluation of inhaled propylene glycol monomethyl ether in rats and rabbits. Fundam. Appl. Toxicol. 4:784-794.

HSDB. 1995. Hazardous Substance Data Bank. National Library of Medicine, Bethesda, Maryland (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc., (Edition expires 1/31/95).

IRIS. 1995. Integrated Risk Information System. (CD-ROM Version). Cincinnati, OH: US Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria Assessment Office.

Landry TD, Gushow TS, and Yano BL. 1983. Propylene glycol monomethyl ether: A 13-week inhalation toxicity study in rats and rabbits. Fundam. Appl. Toxicol. 3:627-630.

Miller RR, Hermann EA, Langvardt PW, McKenna MJ, and Schwetz BA. 1983. Comparative metabolism and disposition of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in male rats. Toxicol. Appl. Pharmacol. 67:229-237.

Miller RR, Hermann EA, Young JT, Landry TD, and Calhoun LL. 1984. Ethylene glycol monomethyl ether and propylene glycol monomethyl ether: Metabolism, disposition and subchronic inhalation toxicity studies. Environ. Health Perspect. 57:233-239.

Rowe VK, McCollister DD, Spencer HC, Oyen F, Hollingsworth RL, and Drill VA. 1954. Toxicology of mono-, di-, and tri-propylene glycol methyl ethers. Arch. Ind. Hyg. Occup. Med. 9:509-525.

Stewart RD, Baretta ED, Dodd HC, and Torkelson TR. 1970. Experimental human exposure to vapor of propylene glycol monomethyl ether: Experimental human exposure. Arch. Environ. Health 20:218-223.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Health and Environmental Effects Profile for Glycol Ethers. Prepared by the office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EP/540/1-86/052. [cited in U.S. EPA, 1995].